REMARKS

Applicants wish to thank Examiner Davis for the opportunity to meet with her for an interview on Friday, September 6, 2002.

Prior to the Office Action mailed May 7, 2002, claims 21, 23, and 25-27 were pending. Upon entry of this amendment, claims 21, 23, 25-29 will be active and pending in this case. Support for new claim 28 can be found in the specification on page 12, line 29 through page 13, line 25, and thus does not constitute new matter.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, SCOPE

In the Final Office Action, the Examiner has maintained rejection of claims 21, 23 and 25 under 35 U.S.C. §112, first paragraph. However, during the interview with the Examiner on September 6, 2002, Applicants clarified that element d) of claim 25 was only an inhibitor of the active compound when bound through element c) and that once cleaved, d) would not exert an inhibitory effect on the active compound. Applicants note that pursuant to the Examiner's instruction at the interview, claim 25 has been amended to clarify this point. Accordingly, Applicants respectfully request withdrawal of this rejection.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT

The Examiner rejects claims 21, 23, and 25-27 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement, for the reasons of record in paper No. 18. The Examiner's arguments essentially fall into two groups. First, the Examiner asserts that "it is not necessarily that any amino acid sequence cleavable by a protease of a construct as broadly claimed in claim 25...is specific for the corresponding protease, e.g. PSA." (Office Action page 4 (emphasis added)). However, as noted during the September 6, 2002 interview, this is a limitation of claim 25. Part c) of the claim requires

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"at least one nucleic acid sequence which encodes an amino acid sequence cleavable specifically by a protease which is released at or from a mammalian target cell." (Emphasis added).

Second, the Examiner maintains that the Cross v. Iizuka case (*in vitro* data supports *in vivo* use) is not applicable to the instant application because the amount of guidance required in a specification is inversely related to the knowledge in the state of the art and the predictability of the art, and there is allegedly "overwhelming evidence in the art that treatment of cancer is unpredictable." Specifically, the Examiner asserts that it is unpredictable that the claimed constructs would be stable *in vivo* and the claimed constructs could be cleaved before reaching the target tissue.

Applicants wish to reiterate that Example 2 discloses a construct that encodes a mutated factor X which cleaves in the presence of PSA and initiates coagulation. Thus, the construct is not intended to destroy the tumor by directly counteracting the nature of the cancer, but through coagulation and depriving the tumor of blood flow. In contrast to the "treatment of cancer," the coagulation pathway is very well known in the art, and has a far greater degree of predictability, and therefore requires less information to be explicitly stated in the specification under MPEP 2164.03.

Further, *in vitro* data in this case clearly demonstrate the stability of the constructs *in vivo*. As shown in Example 2, when the mutated FX was added to FX-deficient plasma in the absence of PSA (negative control), the coagulation time was 200 seconds. In contrast, when mutated FX and PSA were both added to FX-deficient plasma, the coagulation time was 50 seconds, which was similar to the positive control (wild type FX and Russel's vipor venom). This data demonstrates that the mutated FX of the claimed invention is stable in plasma and will not be cleaved prior to exposure to PSA, which is only available at the site of the tumor.

Applicants further traverse the Examiner's assertion of lack of enablement on the basis that the claimed construct has a variety of potential *in vitro* uses. For example, one of skill in the art, based on his technical knowledge at the time the invention was filed would have known that the inventive polypeptides could be used for killing cellular contaminations (target cells) in a cell or tissue culture. The target cells release a protease that specifically recognizes the peptide encoded by the cleavable nucleic acid c). Upon cleavage the active component encoded by the nucleic acid b) is "disinhibited" and will then kill the target cells. As a result, a culture devoid of the target cells is obtained.

In particular, the inventive polypeptides can be applied to remove target cellular contaminations *in vitro* from the blood of patients suffering from a disorder such as prostate cancer. In this preferred example, the hematogenic metastases forming prostate carcinoma cells release the PSA protease which specifically cleaves the peptide encoded by the nucleic acid c). As a result, the active component becomes "disinhibited" and the tumor cells are killed. Alternatively, the same protein could be used to remove prostate carcinoma cells from cell-, tissue-, or organ-culture containing prostate carcinoma cells.

To this end, the person skilled in the art need only refer to the extensive general knowledge about cell/tissue culture or blood purification in addition to the disclosure of the specification, providing a detailed description on how to design such polypeptides according to the invention. Based on the inventive technical teaching of the instant application, such *in vitro* utility can be identified by the person skilled in the art in a way that neither requires inventive activity nor unduly burdensome experimentation in order to enable the *in vitro* use.

CONCLUSION

In view of the above amendment and arguments, Applicants request the withdrawal of all rejections of the pending claims. Applicants further assert that this application is in condition for allowance, and respectfully request rejoinder of claim 19 with the other claims of group II in accordance with MPEP §821.4 and U.S. Patent and Trademark Office Procedure.

Respectfully submitted,

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Date

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